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A Stereospecific Synthesis of 2-Oxabicyclo[3.1.0]hexanes

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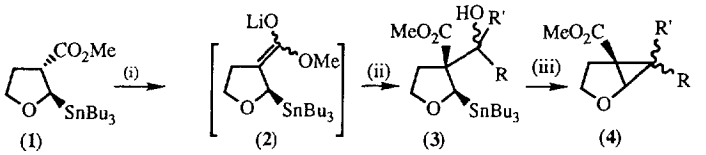
Abstract:- *A stereospecific 1,3-elimination reaction of γ-hydroxy stannanes has been employed in the synthesis of 2-oxabicyclo[3.1.0]hexanes.*

We recently reported[1] that the lithium enolate (**2**) undergoes alkylation reactions with aldehydes and ketones with excellent levels of facial selectivity. As a continuation of our studies in this area we wish to report that the aldol products (**3**) undergo stereospecific 1,3-elimination reactions upon exposure to a variety of Lewis acids to the unusual 2-oxabicyclo[3.1.0]hexane ring system[2] (**4**) in moderate to good yields, **Scheme 1**.

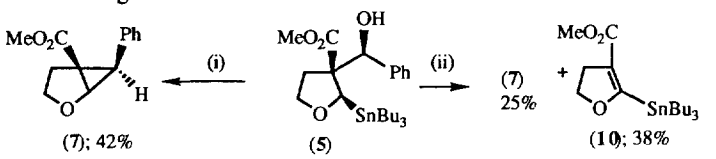


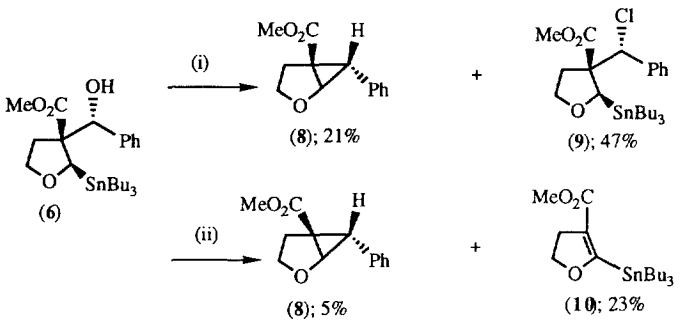
Reagents and conditions:- (i) LDA, 1.1 eq.; THF; -78°C; (ii) RCHO; THF; -78°C; (iii) Lewis acid; THF; 0 °C.

Scheme 1

In our initial experiments, the diastereoisomerically pure alcohols (**5**) and (**6**) were subjected to cyclisation using Johnson's conditions[3] ($SOCl_2$, 3 eq.; pyridine, 4 eq.; THF; 0 °C; 90 mins.). In the case of the *syn*-aldol (**5**), examination of the high field (300 MHz) ^1H nmr spectrum of the crude reaction mixture indicated that clean 1,3-elimination had taken place, affording the 6-*exo*-substituted cyclopropane (**7**) as a single diastereoisomer, **Scheme 2**. Column chromatography afforded cyclopropane[4] (**7**) in an analytically pure state in 42% yield. In the case of the *anti*-diastereoisomer (**6**), cyclisation under the same conditions afforded the 6-*endo*-cyclopropane (**8**) in lower yield (21%) together with the diastereoisomerically pure chloride (**9**) in 47% isolated yield. From mechanistic arguments and ^1H nmr data[5] we tentatively suggest that (**9**) has **2R***, **3R***, **6R*** relative stereochemistry. In an effort to minimise these competing elimination and S_Ni reactions, cyclisation of the alcohols (**5**) and (**6**) was attempted using a variety of promoters. For example, cyclisation of (**5**) and (**6**) with $BF_3.2AcOH$[6] (1.1 eq.; CH_2Cl_2, 0 °C; 30 mins.) afforded the desired cyclopropanes (**7**) and (**8**) in much reduced yields (25% and 5%), together with the formation of the unsaturated ester (**10**) in 38% and 23% isolated

yields respectively, **Scheme 2**. The mechanism for formation of the "oxidative retro - aldol" product (**10**) is currently under investigation.

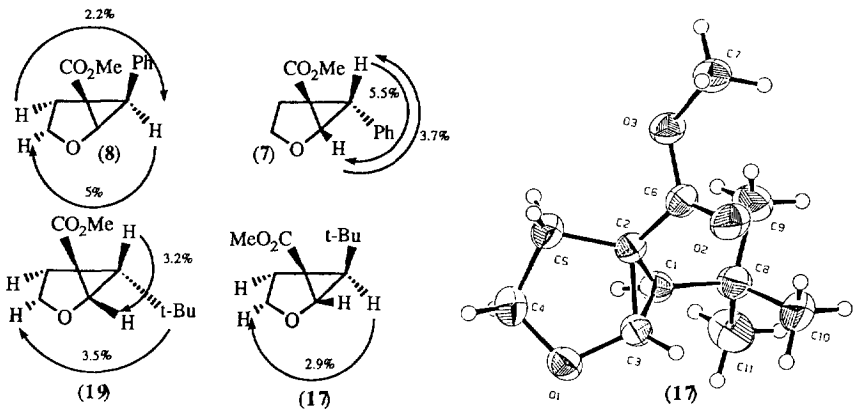




Reagents and conditions: (i) $SOCl_2$, 3 eq.; Pyridine, 4 eq.; CH_2Cl_2; 0 °C; 90 mins.;
(ii) BF_3.2AcOH, 1.1 eq.; CH_2Cl_2; 0 °C, 30 mins.

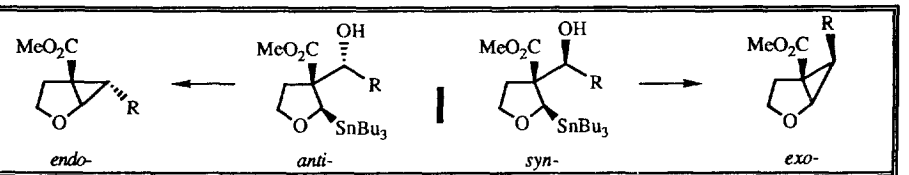
Scheme 2

Further investigations have shown that the 1,3-elimination reaction proceeds best with secondary or benzylic alcohols when using $SOCl_2$/pyridine as promotor, whereas optimum yields for the cyclisation involving tertiary alcohols requires the use of the Lewis acid system developed by Fleming (*i.e.* BF_3. 2AcOH), **Table**. Of note is the observation that high yields of cyclopropanes can be realised when sterically demanding substituents are directly attached to the reacting centres (*e.g.* cyclopropanes (**17**) and (**19**)), even in the case of the 6 - endo substituted cyclopropanes. Stereochemical correlations in this series of compounds are based upon extensive ^1H nmr correlations, and in particular upon the use of nOe difference (NOED) experiments. These correlations are further substantiated by a single crystal X-ray structure determination of the 6 - *exo* - substituted cyclopropane (**17**), **Figure.**



Figure

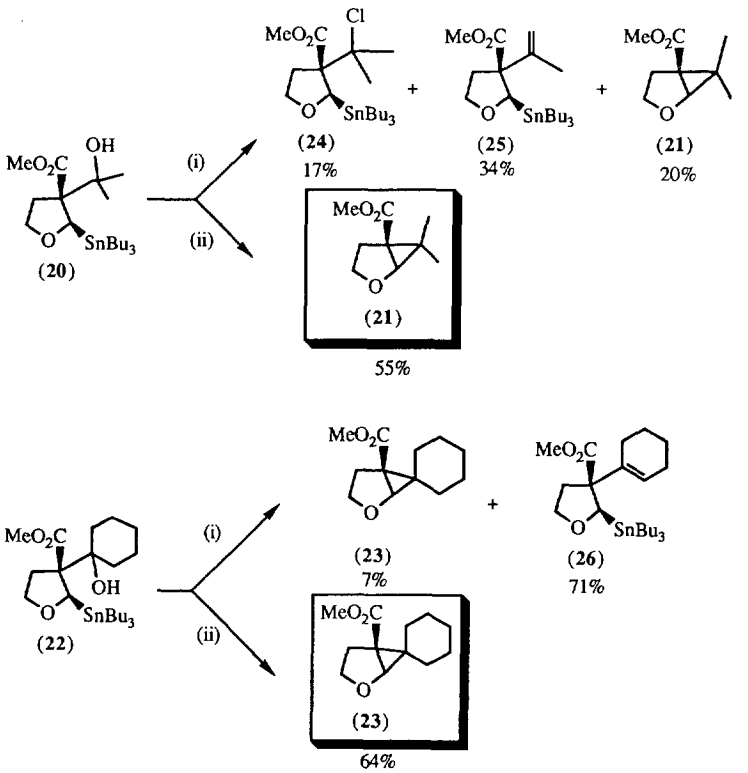
Table



Cyclopropane (),%; Conditions	Alcohol ()$; R =	Alcohol ()$; R =	Cyclopropane (),%; Conditions
(8), 21%; A¶	(6); R = Ph	(5); R = Ph	(7), 42%; A
(8), 5%; B¢	(6); R = Ph	(5); R = Ph	(7), 25%; B∞
(15), 50%; A	(14); R = c -Hxyl	(12); R = c - Hxyl	(13), 48%; A
(19), 52%; A	(18)&; R = t - Butyl	(16); R = t - Butyl	(17), 70%; A

Reaction conditions (A) SO_2Cl_2 (3 eq.); Pyridine (4 eq.); THF; 0 °C; (B) BF_3. 2AcOH (1 eq.) CH_2Cl_2; 0 °C
$ Prepared as in ref. 1. & Prepared as in ref. 8. ∞ Ester (10) also isolated in 38% yield. ¢ Ester (10) also isolated in 23% yield. ¶Chloride (9) also isolated in 47% yield.

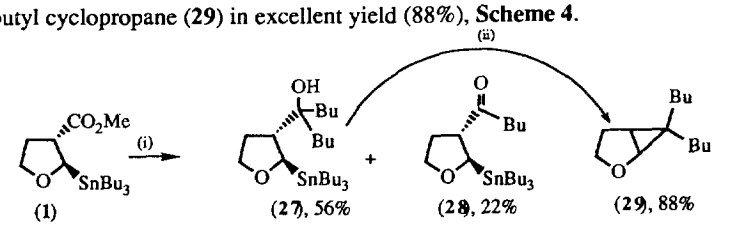
Cyclopropanes possessing two contiguous quatenary centres may also be prepared using this methodology, as exemplified in **Scheme 3**. These examples clearly demonstrate the effect of cyclisation conditions upon the product distribution obtained.



Reagents:- (i) $SOCl_2$ (3 eq.); Pyridine (4 eq.); THF; 0 °C; (ii) BF_3. 2AcOH; CH_2Cl_2; 0 °C.

Scheme 3

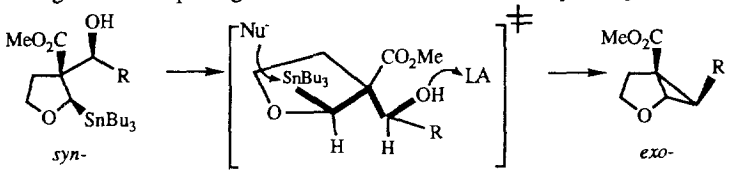
We have also demonstrated that the *trans* - ester (**1**) reacts preferentially at the carbonyl group upon exposure to n - BuLi (n - BuLi, 2.2 eq.; -78 °C; THF) to afford a separable mixture of the carbinol (**27**) (56% yield) and the ketone (**28**) (22% yield). Treatment of (**27**) with BF_3.2 AcOH as above results in the isolation of the gem - di -n- butyl cyclopropane (**29**) in excellent yield (88%), **Scheme 4**.



Reagents and conditions :- (i) n - BuLi (2.2 eq.); THF; -78 °C; (ii) BF_3. 2AcOH, (1.1 eq.); CH_2Cl_2; 0°C.

Scheme 4

In terms of stereochemical outcome, the observation that the *syn* - aldols (**5**), (**12**) and (**16**) give rise to the *exo* - cyclopropanes (**7**), (**13**) and (**17**), whereas the *anti* - aldols (**6**), (**14**) and (**18**) afford the diastereoisomeric *endo* - cyclopropanes (**8**), (**15**) and (**19**) suggests that the reaction proceeds with inversion at both the carbon - tin and carbon-oxygen bonds, presumably *via* a "W"-transition state as originally proposed by Davis[7]. Moreover, the fact that effective promoters ($SOCl_2$; BF_3.2AcOH) of this reaction are capable of activating the - OH group whilst serving as a stannophile gives credence to the notion of a "push - pull mechanism", **Scheme 5**.



Scheme 5

We are currently investigating the chemistry of these "donor - acceptor" cyclopropanes with a view to the synthesis of highly functionalised cyclopropanes in an optically pure state.

Acknowledgements

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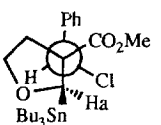
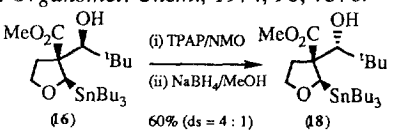
1. Beddoes, R. L.; Lewis, M. L.; Quayle, P.; Zhao, Y. K.; Attwood, M. *Tetrahedron Letters*, **1994**, *35*, 4189.
2. e.g. Christl, M.; Braun, M. *Chem. Ber.*, 1989, **122**, 1939.
3. Johnson, C. R.; Kadow, J. F. *J. Org. Chem.*, 1987, **52**, 1493.
4. All new compounds were fully characterised by high field ^1H and ^{13}C nmr, ir and high resolution mass spectrometry and / or combustion microanalysis.
5. H_a in (**9**) experiences a large downfield shift (*c.a* 1 ppm) compared to the usual chemical shift for this proton, presumably due to the deshielding effect of the chlorine.



(9)

6. Fleming, I.; Urch, C. J. *J. Organomet. Chem.*, 1985, **285**, 173.
7. Davis, D. D.; Johnson, H. T. *J. Organomet. Chem.*, 1974, **96**, 7576.
8. Alcohol (**18**) was prepared from (**16**) in a two - step sequence:-



(16) 60% (ds = 4 : 1) (18)

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